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09/590,211	06/08/2000	Guy A. Rouleau	3028.1000-000	9680

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/590,211	Applicant(s) ROULEAU ET AL.	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *19-30 and 33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is a continuation of PCT/CA98/01133, filed December 7, 1998 which claims benefit to foreign application 2 218 199, filed December 9, 1997 in Canada.

Applicants' amendment filed August 27, 2001, paper number 8, has been received and entered. The specification has been amended.

Election/Restriction

Applicant's election of Group I, claims 1-18, 31 and 32, in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-36 are pending. Claims 19-30 and 33-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claims 1-18, 31 and 32 are currently under examination.

Information Disclosure Statement

A signed copy of the information disclosure statement filed July 12, 2001, paper number 6, is included with the present office action. However, the information disclosure statement filed

May 29, 2001, paper number 5, is not present in the file. Applicants were contacted and a request for the IDS was made by Examiner. Applicants courteously indicated that a copy of the IDS would be faxed as soon as possible and any of the cited references would be provided. It is noted that though the file records indicate that an IDS was received, the information referred to therein has not been considered as to the merits in this instant office action. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). Specifically, the species of $ATG(GCG)_{6+n}GCA$ where n=3 is not represented in the sequence listing. It is noted that the other species encompassed by this recitation $ATG(GCG)_{6+n}GCA$

where n is 1-7 are properly set forth in the sequence listing filed August 27, 2001, paper number 8.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

The disclosure is objected to because of the following informalities: Specifically, the abstract contains the recitation of 'said patient' in line 12. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Additionally, the disclosure is objected to because of the following informalities: In the abstract and the specification, numerous words are hyphenated unnecessarily or misspelled. In the abstract 'pres-ent' at the end of line 9 and 'dis-ease' on 13 have been corrected. In the specification for example, --dystrophy– on line 14 is misspelled 'dys-rophy', dys-phagia' on line 16 is incorrect. Spelling and incorrect hyphenation of words is present throughout the specification.

Appropriate correction is required.

Claim Objections

Claim 32 is objected to because of the following informalities: When the original sequence listing was amended in paper number 8, the sequences set forth in the original sequence listing were given new SEQ ID NOs. Specifically, it appears that the sequence encoding the PABII gene was changed from SEQ ID NO: 3 to SEQ ID NO: 18. This change is also reflected in the amendment to the short description for Figure 4 (page 4 of the instant specification and in paper number 8; page 2). However, claim 32 was not amended to reflect this change in SEQ ID NO. It appears that amending the claim to recite SEQ ID NO: 18 would obviate this objection. Appropriate correction is required.

For the sake of compact prosecution, the claim will be interpreted to be drawn to the gene sequence of the PABII gene set forth in SEQ ID NO: 18.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are drawn to an isolated PABII gene which comprises a polymorphic GCG repeat in exon 1 wherein a variant of said GCG repeat is associated with the symptoms of OPMD in a patient, claims 9-12 are drawn to a nucleic acid sequence comprising a polymorphic GCG repeat in exon 1 of the human PABII gene wherein a variant of said GCG repeat is associated with the symptoms of OPMD, and claims 31 and 32 are drawn to an isolated PABII gene which comprises a polymorphic GCG repeat in exon 1 wherein the variant of said GCG repeat is not associated with the symptoms of OPMD in a patient. Each of the claims are included in the basis of the rejection because of their dependence on the need to clearly set forth a PABII gene or nucleic acid sequences derived therefrom. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

A review of the art of record and the instant disclosure indicates that the only specific nucleic acid sequence which related to human PABII is a cDNA sequence set forth in SEQ ID NO: 18. In the instant case the specification and the art provides adequate written description for the isolated nucleic acid sequences designated by SEQ ID NO: 18, however, the specification fails to adequately describe other nucleic acid sequences which may be encompassed by PABII gene. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case, the specification teaches that the human PABII gene was identified as a gene at a potential candidate loci associated with OPMD. The specification provides an overview of the human PABII gene in figure 1B and the characterization of variant GCG repeats identified in several characterized clones derived from patients with OPMD (in figure 2). The disclosure does not teach any other specific sequence for PABII besides that set forth in SEQ ID NO: 18. The specification teaches that the human PABII gene shares homology with the bovine PABII gene, however neither the art nor the specification discloses that the bovine gene sequence contains GCG repeats or that such repeats are associated with any

particular disease. Even though a depiction of the PABII gene is given in figure 1, the specification fails to provide the specific sequences for the exon/intron borders or intervening sequences encompassed by the instant claims. The disclosure fails to provide a clear description of unique characteristics or features which uniquely define a complete PABII gene. Lacking any specific distinguishing characteristic or features beyond that set forth in SEQ ID NO; 18, the skilled artisan cannot envision any other possible variant nucleic acid sequence besides that set forth in the SEQ ID NO, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Though one may argue that the artisan could easily identify a gene sequence which hybridizes or which is 80% to 98% homologous to SEQ ID NO: 18, it is noted that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In the instant case, though several variant alleles of the PABII with different GCG repeats are taught, 6-13 repeats, only the cDNA sequence for PABII comprising these GCG repeats is taught with particularity as set forth in SEQ ID NO: 18. No other variant is taught besides the GCG repeats, and therefore, the specification fails to provide adequate written description for a PABII

gene or nucleic acid sequence such that the artisan would recognize other sequences besides that set forth in SEQ ID NO: 18.

Therefore, only an isolated nucleic acid sequence as set forth in SEQ ID NO: 18 comprising GCG repeats varying in length from 6 to 13 total repeats meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-17, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human PABII gene comprising a polymorphic GCG repeat which is associated with oculopharyngeal muscular dystrophy (OPMD) disease and uses of said sequence for methods sor the diagnosis and prognosis OPMD in a patient does not reasonably provide enablement for sequences or methods which are indicative of protein accumulation in a cell nucleus, swallowing difficulty or ptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-8 are drawn to an isolated PABII gene which comprises a polymorphic GCG repeat in exon 1 wherein a variant of said GCG repeat is associated with the symptoms of OPMD in a patient, claims 9-12 are drawn to a nucleic acid sequence comprising a polymorphic GCG repeat in exon 1 of the human PABII gene wherein a variant of said GCG repeat is associated

with the symptoms of OPMD, claims 13-17 are drawn to a method of diagnosing or prognosing a disease with symptoms associated with OPMD (claim 18 specifically recites that the disease is OPMD and thus, is not subject to the instant rejection), and claims 31 and 32 are drawn to an isolated PABII gene which comprises a polymorphic GCG repeat in exon 1 wherein the variant of said GCG repeat is not associated with the symptoms of OPMD in a patient. The instant disclosure teaches a cDNA for the PABII gene (set forth in SEQ ID NO: 18) and has characterized a variant GCG repeat in said sequence wherein repeats of seven or more are associated with oculopharyngeal muscular dystrophy (OPMD). The instant specification and the art teaches that patients with OPMD have the symptoms of protein accumulation in a cell nucleus, swallowing difficulty and ptosis, however the instant specification fails to provide the nexus between patients with OPMD and patients with other disease that have one of more of the instantly claimed symptoms. The basis of the instant rejection is drawn to the fact that the PABII variants are specifically associated with only OPMD, and not other diseases with different etiology but that demonstrate one or more similar symptoms.

The basis of the instant invention is based on the observation that patients with OPMD share a common genetic linkage. The instant disclosure and the art teaches that through pedigree analysis a dominant marker for OPMD was defined that maps to chromosome 14q11.2-q13 (for example Stajich *et al.* (1997)). Grewal *et al.* (1998) provides a more refined mapping of the genetic linkage describing specific loci markers within this region of chromosome 14 (summarized on page 962, Table 1). Subsequently, Brais *et al.* (Nature Gentics, 1998 and Sem

Neuro, 1999) as taught in detail in the instant disclosure have identified the PABII gene at this particular loci. DNA analysis of the encoded PABII gene from patients with OPMD demonstrated that a particular number of GCG repeats in the PABII sequence could be correlated to patients with OPMD. A more refined study of the OPMD patients demonstrates that specific combination of alleles of the variant PABII gene are associated with different progression and severities of the disease. In summary, the instant disclosure provides clear evidence that GCG variants of the PABII gene are associated with OPMD. However, the art of record and the instant disclosure fail to provide a nexus between this genetic disorder which has the symptoms of protein accumulation in a cell nucleus, swallowing difficulty and ptosis. For example, a patient with Alzheimer disease demonstrates plaque formation in particular cells in the brain, however the art failure well supports that this protein accumulation is dues to genetic variants of AAP and Tau genes, as well as other genes that affect the post-translation modification of the proteins found in the plaques. Difficulty swallowing and ptosis are very general and common symptoms associated with many diseases with a diverse known etiology. For example, a patient suffering from strep throat would have difficulty swallowing because of the pain associated with disease. Patients who suffer from a stroke, or other conditions which give rise to paralysis, can loose their ability to swallow and often exhibit drooping on the opposite side of the lesion. Clearly, the art teaches and the skilled artisan knows that many diseases exhibit the above describe symptoms. Further, the etiology of these symptoms is fairly well defined for a particular disease. In the instant case, the instant disclosure has established that a particular set of GCG repeats in the

PABII gene is associated with patients who have been diagnosed with OPMD, however the disclosure fails to provide a nexus between this genetic link and specific disease, and any other disease which exhibits the symptoms of protein accumulation in a cell nucleus, swallowing difficulty and ptosis.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to practice the full scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 5 and 6 are confusing and lack sufficient antecedent basis for a first and second allele in claim 1. It is noted that claim 1 is drawn to 'An isolated human PABII gene' and recites 'an allelic variant', however claims 5 and 6 seem to be drawn to more than one sequence contained in a single gene. Examiner recognizes that the instant specification teaches certain combinations of alleles in a human subject produce various severities of OPMD, however the instant claims are drawn to single and separate genes outside an individual. Reciting a first and

second allele is confusing because any one isolated PABII gene will only represent one particular sequence. Amending the claims to recite that an allele has a 'n which is equal to 1' and 'n selected from 2 to 7' would obviate the basis of the rejection. Alternatively, amending the claim to reflect that the first and second allele of 'said human patient comprising said GCG repeat' to clearly indicate that the multiple alleles are present in the patient would obviate the basis of the rejection.

Claim 9 is vague and unclear in the recitation of 'nucleic acid sequence comprising a polymorphic GCG repeat of exon I of a human PABII gene' because it is unclear if the claim is drawn only to the GCG repeat, the GCG sequence in context of the PABII gene or the GCG in the context of exon 1. Dependent claim 10 sets forth a specific consensus sequence for the GCG, and claims 11 and 12 set forth what a particular phenotype in a patient associated with a particular variant, are included in the basis of the rejection because none of the claims further clarify the metes and bounds of the particular nucleic acid which is being claimed in independent claim 9. It is unclear if a sequence meeting the limitation of being a GCG repeat would meet the limitations of the claim, even if it were derived from a sequence other than the PABII gene. More clearly setting forth the particular sequence encompassed by the claim, such as by a SEQ ID NO, would obviate the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Akarsu *et al.* (Hum Mol Gen 5(7):945-952, 1996).

As noted above in the 35 USC 112, second paragraph, rejection, the metes and bounds of the nucleic acid encompassed by a GCG repeat is unclear, and could reasonably be interpreted to encompass only a GCG repeat. Akuarsu *et al.* teach a polyalanine duplication which is the result of 9 GCG repeats in the (see page 947; Figure 2). This repeat is present in a human gene and is associated with synpolydactyly. Though, this disease does not share the same symptoms as OPMD, the GCG repeat is nine repeats long and would meet the limitations of a GCG repeat associated with OPMD. Therefore, the GCG repeat taught by Akarsu *et al.* anticipates the GCG repeat as instantly claimed.

Conclusion

No claim is allowed. Claims 1-8, 10-18, 31 and 32 are free of the art of record, however they are subject to other rejections. Claim 18 is objected to because it is dependent on a rejected claim, however would be found allowable if rewritten in independent form encompassing all the limitations of the independent claim and any intervening claims. The instant disclosure teaches a

cDNA for the PABII gene(set forth in SEQ ID NO: 18) and has characterized a variant GCG repeat in said sequence wherein repeats of seven or more are associated with oculopharyngeal muscular dystrophy (OPMD).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Patsy Zimmerman whose telephone number is (703)308-8338.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

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